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Effect of blood pH on distal nephron hydrogen ion secretion

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Effect of blood pH on distal nephron hydrogen ion secretion. The purpose of this study was to determine the effect of changes in blood hydrogen ion concentrations on urine acidification. The urine minus the blood P_{CO_2} gradient in alkaline urine was used to monitor distal nephron hydrogen ion secretion. To obtain alkaline urine during acidemia, we induced proximal renal tubular acidosis by lysine. The urine minus the blood P_{CO_2} gradient was evaluated relative to the urine bicarbonate concentration over a range of blood pH values. For any given urine bicarbonate concentration, the urine minus the blood P_{CO_2} gradient was directly related to the blood hydrogen ion concentration. *Conclusions.* Acidemia stimulates and alkalemia inhibits distal nephron hydrogen ion secretion. Because the slope relating the urine minus the blood P_{CO_2} gradient to the urine bicarbonate concentration was much steeper in urine from acidemic dogs, this change in relationship cannot be explained by a simple chemical equilibrium of the bicarbonate buffer system.

Effet du pH sanguin sur la sécrétion d'ion hydrogène par le néphron distal. Le but de ce travail est de déterminer l'effet des modifications de la concentration sanguine des ions hydrogène sur l'acidification de l'urine. Le gradient de P_{CO_2} urine moins sang en urine alcaline a été utilisé pour évaluer la sécrétion d'ions hydrogène par le néphron distal. Afin d'obtenir une urine alcaline au cours de l'acidémie, une acidose tubulaire proximale a été induite par la lysine. Le gradient de P_{CO_2} urine moins sang a été évalué en fonction de la concentration de bicarbonate dans un éventail de valeurs de pH du sang. Pour une concentration de bicarbonate de l'urine donnée le gradient est directement lié à la concentration d'ions hydrogène dans le sang. *Conclusions.* L'acidémie stimule et l'alcalémie inhibe la sécrétion distale d'ions hydrogène. Puisque la pente qui relie le gradient de P_{CO_2} urine moins sang à la concentration de bicarbonate de l'urine est beaucoup plus grande dans l'urine de chiens acidémiques, une simple modification de l'équilibre chimique du système tampon bicarbonate ne peut expliquer la modification de la relation.

The urine minus the blood P_{CO_2} gradient in alkaline urine (U-B P_{CO_2}) has been used as a qualitative index of hydrogen ion secretion in the distal nephron in vivo [1]. Several factors in addition to distal hydrogen ion secretion may influence this parameter. Of these, the most important is the urine bicarbonate concentration [2–5]. In addition, the urine buffer capacity [6, 7], the blood P_{CO_2} [8], and the plasma potassium concentration [9] may also alter the U-B P_{CO_2}. In virtually all studies utilizing the U-B P_{CO_2} reported to date, alkalemia has been present, of necessity, because urine alkalinization was achieved by means of bicarbonate administration leading to metabolic alkalosis. We initiated the present investigations to evaluate the possible independent effect of acidemia or alkalemia on distal nephron hydrogen ion secretion as measured by the U-B P_{CO_2}. To obtain alkaline urine in the presence of acidemia, we induced proximal renal tubular acidosis (RTA) in dogs by the infusion of lysine [10–12], arginine [13], or ornithine [13]. The results indicate that the U-B P_{CO_2} is significantly increased during acidemia and decreased during alkalemia. Thus, the acid-base status of the animal exerts a significant independent effect on distal hydrogen ion secretion as monitored by the U-B P_{CO_2}.

Methods

Studies were carried out on 44 female mongrel dogs ranging in weight from 12 to 30 kg, with a mean weight of 20 kg. Food was withheld for 20 hours before each study, but the animals were allowed free access to water. Dogs were anesthetized with sodium pentobarbital (30 mg/kg body wt, i.v.) and received subsequent small doses whenever necessary during the experiments. A cuffed endotracheal tube was introduced into the trachea and connected to a Harvard ventilator. The rate and depth of respiration were initially adjusted to maintain arterial P_{CO_2} at approximately 35 mm Hg. During the remainder of the experiments, no further adjustments were made on the respirator.

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The bladder was catheterized, and urine was collected under mineral oil through an indwelling Foley catheter. Manual pressure over the suprapubic area was used to empty the bladder at the end of each collection period. Blood samples were drawn anaerobically at the midpoint of each 20-min collection period through a femoral artery indwelling catheter, and these were analyzed immediately for acid-base parameters. A priming dose of creatinine (20 mg/kg) was administered and followed by a solution of 5% mannitol containing 25 g of creatinine and 2 g of PAH per liter. This solution was infused throughout each experiment at a constant rate of 2 ml/min into the femoral vein. After a 90-min equilibration period, three consecutive 20-min control clearance periods were obtained. Nine 20-min clearance periods were analyzed in each animal over the course of the 180-min infusion of either lysine, arginine, or ornithine. Three groups of dogs were studied.

Group 1: Lysine-induced proximal renal tubular acidosis (RTA) in the presence of acidemia. L-Lysine (pH, approx. 7.4) was infused at a rate of 55 μmoles/kg/min to 14 dogs and at the rate of 110 μmoles/kg/min to 12 additional dogs. A large number of animals was required for this group, to obtain sufficient data points with high urine bicarbonate concentrations during acidemia.

Group 2: Lysine-induced proximal RTA in the absence of acidemia. To prevent any signficant change in plasma acid-base parameters, 5 dogs were given 55 μmoles/kg/min of 0.5 M L-lysine (pH, 9.8). We infused L-lysinate (pH, 12) at a dose of 55 μmoles/kg/min to 5 additional dogs to induce simultaneously alkalemia and an alkaline urine. Sodium hydroxide (2 N) was used to raise the pH of the L-lysine solutions.

Group 3: Arginine or ornithine-induced proximal RTA in the presence of acidemia. This protocol was designed to determine whether other cationic amino acids such as arginine and ornithine could reproduce the results seen with lysine. Accordingly, L-arginine (pH, 7.4) was infused at a dosage of 110 μmoles/kg/min into 3 dogs, and L-ornithine (pH, 7.4) was infused at a rate of 55 μmoles/kg/min into 5 dogs.

To prevent the generation of a high urine P_{CO_2} from mixing of acid and alkaline urines in the lower urinary tract [6, 7, 14], we accepted urine samples only if the pH of the preceding urine did not differ by more than 0.20 pH unit. For the same reason, urine samples containing less than 20 mM bicarbonate were discarded.

Analytical methods and calculations. The pH and P_{CO_2} of blood and urine were measured anaerobically at 38° C with a digital acid-base analyzer (model PHM 72, Radiometer). The plasma bicarbonate concentration was calculated from the Henderson-Hasselbalch equation. A pK′ of 6.10 was used for carbonic acid, and a solubility factor of 0.0301 was used for carbon dioxide. In the urine, a solubility coefficient of 0.0309 was used, and the pK′ calculated from urinary ionic strength was $6.33 - 0.5 \sqrt{(Na^+) + (K^+)}$, the concentrations of sodium and potassium being expressed in equivalents per liter [15].

The concentrations of sodium and potassium in blood and urine were measured by flame photometry. Chloride was determined with a chloridometer (Buchler-Cotlove). An autoAnalyzer (Technicon) was used to measure phosphate, creatinine, and PAH. The method of Fiske and Subbarow was used to measure phosphate [16]; the method of Chasson, Grady, and Stanley, for creatinine [17]; and the method of Smith et al, for PAH [18]. A manometer (Warburg) was used to determine the L-lysine concentration with L-lysine decarboxylase [19]. Urine buffer capacity was measured by the back titration of bicarbonate-free urine from a pH of 4.5 to 8.5 with sodium hydroxide (0.1 N) and was recorded as the alkali added per unit of pH change as described by Halperin et al [1]. Creatinine clearance was used to estimate the GFR. Renal blood flow was calculated from the PAH clearance as previously described [12].

Materials. L-Lysine monochloride was obtained from Eastman Kodak Co., Rochester, New York. L-Arginine monohydrochloride, L-ornithine monohydrochloride, L-lysine decarboxylase, creatinine, and PAH were obtained from Sigma Chemical Co., St. Louis, Missouri. Sodium pentobarbital was obtained from Abbott Laboratories, Ltd., Montreal, Canada. All other chemicals used were of the highest chemical grade of purity.

Statistical analysis. The regression lines were calculated by the method of least squares. The slopes of the various regression lines were compared by the analysis of covariance as described in Snedecor and Cochran [20].

Results

Because the infusion of various ionic forms of lysine resulted in widely varying blood pH values, dogs having a blood pH exceeding 7.43 (alkalemia) and dogs with a blood pH lower than 7.36 (acidemia) were analyzed separately. In both groups of

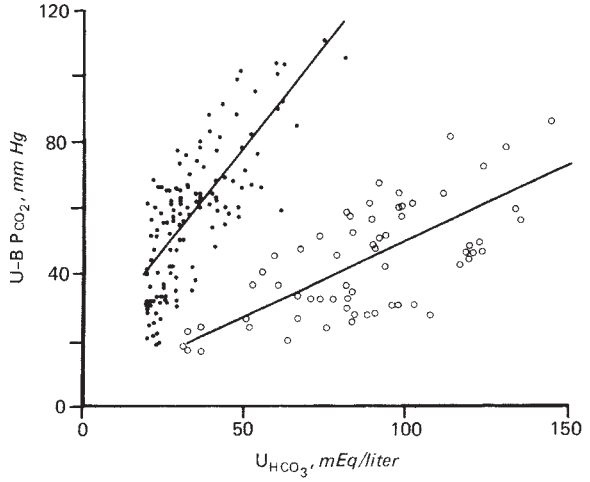

Fig. 1. *Effect of urine bicarbonate concentration on the U-B P_{CO_2} during lysine infusion into dogs with a blood pH exceeding 7.43 or less than 7.36.* For details, see Methods and Tables 1 and 2. The regression line during alkalemia *(open circles)* is U-B P_{CO_2} = 0.47 U_{HCO_3} + 3.9, N = 64, r = 0.74, $P < 0.01$, whereas the regression line during acidemia *(closed circles)* is U-B P_{CO_2} = 1.26 U_{HCO_3} + 14.7, N = 141, r = 0.76, $P < 0.01$.

dogs, a correlation was observed between the U-B P_{CO_2} and the urine bicarbonate concentration, as was previously shown for normal dogs [2–5]. In alkalemic dogs, the individual data for the U-B P_{CO_2}, plotted as a function of the urine bicarbonate concentration, are shown as the open circles in Fig. 1; the linear regression was U-B P_{CO_2} = 0.47 U_{HCO_3} + 3.9 (N = 64, r = 0.74, $P < 0.01$). During acidemia (closed circles of Fig. 1), the regression equation was U-B P_{CO_2} = 1.26 U_{HCO_3} + 14.7 (N = 141, r = 0.76, $P < 0.01$). At all levels of urinary bicarbonate concentration, the U-B P_{CO_2} was much higher during acidemia than it was during alkalemia; consequently, the slope of the linear regression for the U-B P_{CO_2} versus the urine bicarbonate concentration was much steeper during acidemia than it was during alkalemia. These two slopes were significantly different from each other ($P < 0.01$) when examined by covariance analysis.

Table 1 presents the time course of one representative experiment in which the infusion of L-lysine (pH, 7.4) resulted in acidemia, and the infusion of sodium L-lysinate (pH, 12) induced alkalemia. Table 2 contains pertinent blood and urine values for the acidemic, normal (blood pH, 7.36 to 7.43) and alkalemic groups of dogs infused with lysine. A single value for each dog, obtained by averaging all the observations during lysine infusion, was used to calculate the group means and standard errors.

From the data presented in Tables 1 and 2, the U-B P_{CO_2} observed in acidemic dogs was higher than it was in alkalemic dogs despite their much lower urine bicarbonate concentration. It is noteworthy that the U-B P_{CO_2} changes appear to reflect changes in urine bicarbonate concentration and blood pH rather than urine phosphate or lysine concentrations. Arterial P_{CO_2} remained around 35 mm Hg unless acidemic was present. Plasma lysine con-

Table 1. Representative experiments depicting effects of lysine infusion during acidemia and alkalemia[a]

Blood				Urine							
pH	P_{CO_2} *mm Hg*	HCO_3 *mEq/liter*	Lysine *mM*	pH	P_{CO_2} *mm Hg*	HCO_3 *mEq/liter*	$\dot{V}$ *ml/min*	PO_4 *mM*	Lysine *mM*	GFR *ml/min*	U-B P_{CO_2} *mm Hg*
					Acidemia						
7.40	36	22	—	7.11	32	8	0.9	0.1	—	63	−4
7.41	34	21	0.5	7.49	32	19	1.3	0.1	0.3	68	−2
Start infusion of L-lysine monohydrochloride, 55 μmoles/kg/min											
7.38	34	19	3	7.50	51	31	1.8	0.1	40	65	17
7.38	32	18	—	7.53	84	54	2.3	0.1	—	61	52
7.36	32	17	7	7.48	112	66	3.1	0.1	68	55	80
7.32	32	16	—	7.45	117	66	3.7	0.1	—	52	85
7.32	31	16	—	7.39	122	60	4.6	0.3	—	51	91
7.28	29	13	9	7.36	112	53	5.3	0.5	74	59	83
					Alkalemia						
7.35	41	22	—	6.07	49	1	0.6	0.3	—	59	8
7.34	39	20	0.5	6.05	49	1	0.6	0.3	0.1	56	10
Start infusion of sodium L-lysinate, 55 μmoles/kg/min											
7.43	39	25	—	7.69	66	66	1.4	0.2	—	76	27
7.46	42	29	—	7.75	101	133	4.6	0.1	—	59	59
7.51	41	31	8	7.77	98	135	8.3	0.1	33	61	57
7.52	41	32	—	7.77	84	116	11.5	0.1	—	53	43
7.51	43	34	—	7.76	89	120	13.1	0.1	—	58	46
7.54	41	34	17	7.75	89	118	12.0	0.1	52	52	48

[a] Results were recorded at 20-min intervals. For details, see Methods.

centrations were comparable in the three groups of dogs, but urine lysine concentrations were higher during acidemia than they were during alkalemia (Table 2). Urine phosphate concentrations remained negligible in all lysine-infused dogs but mean GFR and mean renal blood flow were comparable in all three groups of animals.

To document that the results reported in Fig. 1 could not be attributed to the higher urine lysine concentration or plasma potassium concentration during acidemia, we analyzed the results at comparable values for these parameters. As shown in Table 3, the U-B P_{CO_2} factored for the urine bicarbonate concentration was higher during acidemia despite similar urine lysine and plasma potassium concentrations.

In an attempt to demonstrate that the higher U-B P_{CO_2} for a given urine bicarbonate concentration was not specific for lysine, we also induced proximal RTA by arginine or ornithine. The vast majority of values for the U-B P_{CO_2} versus the urine bicarbonate concentrations obtained during acidemia during arginine and ornithine infusion were within the 95% confidence limits for the U-B P_{CO_2} established when acidemia was present during lysine infusion (Fig. 2), suggesting that the effect of blood pH on the U-B P_{CO_2} was not specific for lysine.

The urine buffer capacity, measured in dogs infused with ornithine and for the urine pH range of the samples (6.5 to 7.5), was 6.4 ± 1.8 μEq/ml (N = 14 samples) before ornithine infusion and rose only to 7.8 ± 0.7 μEq/ml following ornithine infusion (N = 35 samples).

These studies suggest that the blood pH might be an important factor in influencing the U-B P_{CO_2} at any given urine bicarbonate concentration. This impression was confirmed when a striking relationship was found between the U-B P_{CO_2} factored for the urine bicarbonate concentration and the blood hydrogen ion concentration (Fig. 3). This relationship was described by the linear regression U-B P_{CO_2}/U_{HCO_3} = 0.046 blood $[H^+]$ − 0.87, (N = 249, r = 0.86, $P < 0.01$).

Discussion

We have demonstrated previously that the U-B P_{CO_2} can be used as a qualitative index of distal nephron hydrogen ion secretion providing that several precautions are taken [1]. Accordingly, the pH

Table 2. Effect of blood pH on urine acid-base parameters in dogs infused with lysine[a]

	Blood					Urine							
Blood pH	pH	P_{CO_2} *mm Hg*	HCO_3 *mEq/liter*	K^+ *mEq/liter*	Lysine *mM*	pH	P_{CO_2} *mm Hg*	HCO_3 *mEq/liter*	$\dot{V}$ *ml/min*	PO_4 *mM*	Lysine *mM*	GFR *ml/min*	U-B P_{CO_2}/U_{HCO_3}
<7.36	7.28	31	14	4.8	12	7.27	85	32	5	<1	83	58	1.75
	±0.01	±1	±1	±0.1	±1	±0.02	±4	±2	±1		±7	±4	±0.04
7.36 to 7.44	7.42	35	22	4.0	9	7.64	101	97	5	<1	65	53	0.97
	±0.01	±4	±1	±0.2	±1	±0.03	± 7	± 5	±1		±5	±10	±0.06
>7.44	7.53	35	28	3.0	9	7.75	79	99	9	<1	35	49	0.52
	±0.03	±3	±2	±0.1	±1	±0.02	±12	±14	±1		±6	±6	±0.02

[a] For details of lysine infusions, see Methods. Results are reported as the means ± SEM. The number of dogs was 26, 5, and 5 in the acidemic, normal blood pH, and alkalemic groups, respectively.

Table 3. Effect of blood hydrogen ion concentration on the U-B P_{CO_2} corrected for the urine bicarbonate concentration: Role of urine lysine and plasma potassium concentrations[a]

	Blood $[H^+]$ *nEq/liter*	Urine lysine *mM*	P_K *mEq/liter*	U-B P_{CO_2}/U_{HCO_3} *mm Hg/mM*
Series A				
Acidemic (9)	54 ± 4	58 ± 3	—	1.42 ± .22
Alkalemic (10)	33 ± 1[b]	51 ± 2	—	0.56 ± .05[b]
Series B				
Acidemic (14)	51 ± 1		3.8 ± 0.1	1.33 ± .07
Alkalemic (16)	34 ± 1[b]		3.7 ± 0.1	0.64 ± .02[b]

[a] Dogs were selected on the basis of a urine lysine concentration of 40 to 70 mM in series A and a plasma potassium concentration of 3.5 to 4.0 mEq/liter in series B. They were divided into two groups on the basis of a blood hydrogen ion concentration of greater than 44 nEq/liter or less than 37 nEq/liter. The number of observations is shown in parentheses. Results are reported as the means ± SEM.
[b] $P < 0.01$.

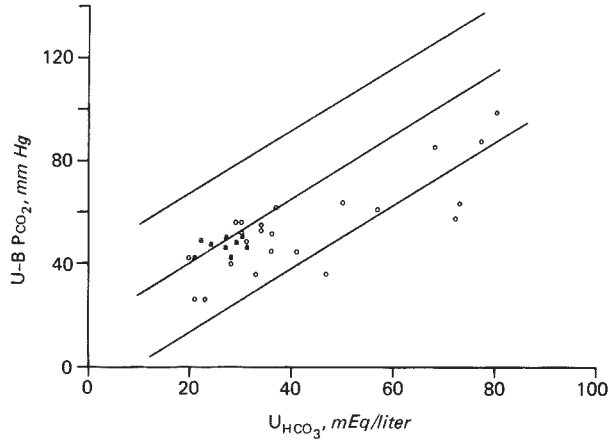

Fig. 2. *Effect of urine bicarbonate concentration on the U-B P_{CO_2} during arginine* (letter a) *and ornithine* (letter o) *infusion when blood pH was less than 7.36.* The 95% confidence limits for individual points for the U-B P_{CO_2} vs. urine bicarbonate concentration when blood pH was less than 7.36 during lysine infusion are shown.

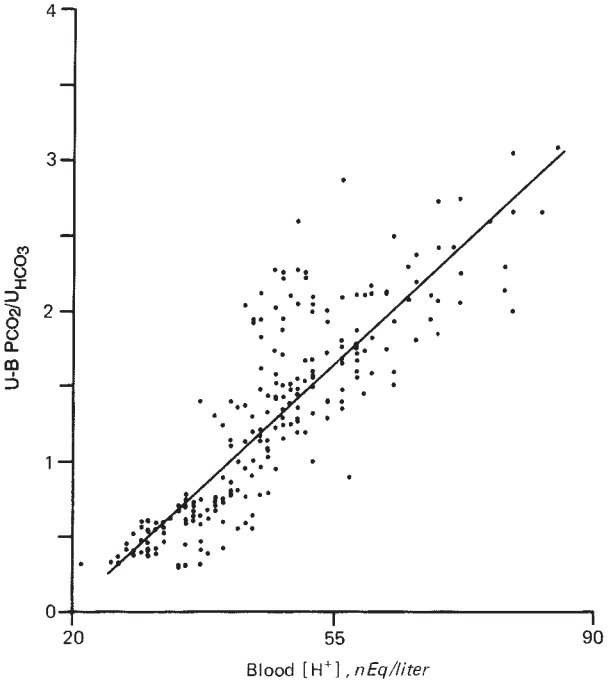

Fig. 3. *Effect of blood hydrogen ion concentration on the U-B P_{CO_2} factored by the urine bicarbonate concentration.* The data in this figure were derived in part from Fig. 1 as well as additional data when the blood pH was between 7.36 and 7.42. The regression line is U-B P_{CO_2}/U_{HCO_3} = 0.046 blood $[H^+]$ − 0.87, N = 249, r = 0.86, $P < 0.01$.

of the preceding urine must be similar to the one in the experimental period, thereby avoiding the generation of a high P_{CO_2} as a consequence of the mixing of acid and alkaline urine in the lower urinary tract [14]. In addition, urine samples containing less than 20 mM bicarbonate should not be used for U-B P_{CO_2} measurements. Furthermore, because hypocapnia was associated with a low U-B P_{CO_2} [8], the arterial blood P_{CO_2} was maintained at about 35 mm Hg by artificial ventilation unless metabolic acidosis was present. Last, because the bicarbonate concentration in the urine can influence the U-B P_{CO_2} [3–5], the U-B P_{CO_2} was evaluated relative to the urine bicarbonate concentration.

The U-B P_{CO_2} can be determined by at least two factors: the urine bicarbonate concentration [3–5] and the distal nephron hydrogen ion secretion [1]. The mechanism by which urine bicarbonate elevates the urine P_{CO_2} is a matter of conjecture. Maren [21] and Arruda et al [4] have postulated that the "ampholyte effect of bicarbonate," a physical-chemical process independent of hydrogen ion secretion, is the principal cause for the high U-B P_{CO_2}. If this were the case, then the relationship between the U-B P_{CO_2} and the urine bicarbonate concentration would be described by a regression line with a predictable unique slope. As can be seen in Fig. 1, however, the slope of this regression line was significantly higher in acidemia. Therefore, these data cast doubt on the assumption that the linear relationship between the U-B P_{CO_2} and the urine bicarbonate concentration was due simply to the ampholyte effect of bicarbonate. It follows that the higher U-B P_{CO_2}/bicarbonate ratio during acidemia must be related to another factor, such as the distal nephron hydrogen ion secretion. It appears that this latter component was increased during acidemia.

Lysine may have been able to stimulate distal nephron hydrogen ion secretion for reasons other than acidemia. Cationic buffers such as Tris have been reported to elevate the U-B P_{CO_2} [6, 7, 14], presumably as a consequence of an increase in urine buffer capacity. Because the pK'_2 for lysine (8.95) is almost 2 pH units higher than the urine pH in our studies and because the maximum urine lysine concentration rose to about 75 mM, it is unlikely that lysine increased the U-B P_{CO_2} as a result of an increased urine buffer capacity. In fact, there was only a minimal increase in the urine buffer capacity in 35 samples after ornithine infusion into acidemic dogs, in which the U-B P_{CO_2} rose appreciably (see Results). Furthermore, when the urine lysine concentrations were similar during acidemia and alkalemia, the U-B P_{CO_2} factored for the urine bicarbonate concentration was significantly higher during acidemia (Table 3).

In a moderately alkaline urine, phosphate may play an important role in elevating the U-B P_{CO_2},

presumably by contributing to buffer capacity. In these studies, however, the urine phosphate was low and not influenced by acid-base state (Tables 1 and 2). Therefore, the large increase in U-B P_{CO_2} cannot be attributed to urine phosphate or buffer capacity.

Lysine caused the plasma potassium concentration to be elevated (Table 2) [10–13]. An elevated plasma potassium concentration did not increase the U-B P_{CO_2} in experiments in dogs [3]. Furthermore, as shown in Table 3, the U-B P_{CO_2} factored for the urine bicarbonate concentration was higher during acidemia at a time when the plasma potassium concentration was not different from that in alkalemia.

To exclude the possibility that the rise in U-B P_{CO_2} following lysine infusion was a specific effect of lysine, we studied the effects of ornithine and arginine on the U-B P_{CO_2} during acidemia. The U-B P_{CO_2} was again higher at any given urine bicarbonate concentration when acidemia was present. The results were consistent with the general hypothesis that acidemia stimulated distal nephron hydrogen ion secretion. In human patients with proximal RTA, acidemia, and an alkaline urine, the U-B P_{CO_2} at a given urine bicarbonate concentration was higher than it was during alkalemia. For example, the U-B P_{CO_2} was 80 mm Hg (upper limit of expected values being 55 mm Hg) when the urine bicarbonate was 90 mEq/liter in a patient with hereditary fructose intolerance [22]. In four patients with proximal RTA acidemia and alkaline urine, reported by Latner and Burnard [23], the U-B P_{CO_2} was about 1.5-fold higher than the upper limit of normal compared to normals with equal urine bicarbonate concentrations.

Lysine appeared to depress proximal bicarbonate reabsorption, presumably by inhibiting hydrogen ion secretion [10–13]. On the other hand, the present results imply that distal nephron hydrogen ion secretion was relatively unimpaired during lysine administration. One possible explanation is that an appreciable quantity of lysine did not gain entry into the distal nephron cells. Microinjection studies in rats have shown that lysine reabsorption took place exclusively in the proximal tubule and that lysine, when injected into the distal tubular lumen, was excreted quantitatively in the urine [24]. Therefore, it is unlikely that lysine reabsorption in its nonionized form was responsible for elevating the U-B P_{CO_2}.

In summary, the results presented in this paper are consistent with the hypothesis that alterations in the systemic acid-base status influenced distal nephron hydrogen ion secretion.

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